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(54) Title: STABLE ORAL BENZIMIDAZOLE COMPOSITIONS AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: The present invention relates to stable oral benzimidazole compositions and processes for their preparation. The stable oral benzimidazole pharmaceutical composition includes a core, a separating layer, and an enteric coating. The core includes a benzimidazole compound, a substantially water-soluble material and, optionally, one or more pharmaceutically acceptable excipients, wherein the core is not alkaline. The separating layer surrounds the core and includes a substantially water-soluble material and, optionally, one or more pharmaceutically acceptable excipients. The enteric coating surrounds the separating layer. At least one of the core and the separating layer includes the substantially water-soluble material without any pharmaceutically acceptable excipients.

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STABLE ORAL BENZIMIDAZOLE COMPOSITIONS AND PROCESSES FOR THEIR PREPARATION

Field of the Invention

The present invention relates to stable oral benzimidazole compositions and processes for their preparation.

Background of the Invention

U.S. Patent Nos. 4,255,431, 4,628,098 and 4,758,579 disclose substituted pyridylsulfinyl benzimidazoles as potent inhibitors of gastric acid secretion. This class of compounds inhibits gastric acid secretion by inhibiting H^+-K^+ ATPase (proton-pump) activity. Drugs in this class are known to be highly unstable in an acidic environment. They are also unstable in the presence of moisture and organic solvents. Thus, the formulation in which the drugs are to be administered to a patient, and the process for manufacture of the formulation, must be designed to protect the drug from moisture as well as an acidic environment. Due to the rapid drug degradation that occurs in acidic gastric fluids, the formulations may be enteric coated.

The stability problems associated with benzimidazole compounds are well recognized in the prior art, which teaches various approaches to preparing stable formulations containing benzimidazole compounds. One of the most common approaches utilized to stabilize benzimidazole compounds is the use of an alkaline core, a separating layer and an enteric coating. It is well-recognized in the art that use of an alkaline medium within the core protects benzimidazole compounds from acid degradation. Previous attempts to stabilize formulations of benzimidazole compounds were ineffective when using an alkaline core without a separating layer between the core and the enteric coating. Thus, the need for a separating layer between the core and enteric coating. An example of the use of a separating layer between the alkaline core and the enteric coating is described in U.S. Patent No. 4,786,505 and U.S. Patent No. 4,853,230. The separating layer disclosed is made of water-soluble polymeric substances.

U.S. Patent No. 5,035,899 discloses a peroral preparation of a benzimidazole compound that is described as consisting essentially of a core, a slightly water soluble first

coating layer, and a second coating layer. The core contains a pharmacologically effective, acid-unstable benzimidazole compound. The first coating layer is coated on the core and includes a slightly water-soluble, film-forming material selected from the group consisting of ethyl cellulose and polyvinyl acetate and fine particles of a slightly water-soluble substance selected from the group consisting of magnesium oxide, silicic anhydride, calcium silicate, magnesium hydroxide, magnesium carbonate, aluminum hydroxide, calcium stearate, magnesium stearate and sucrose fatty acid esters suspended in the first layer. The second coating layer is coated on the first layer and is made of an enteric polymer film.

U.S. Patent No. 6,274,173 discloses a controlled release pharmaceutical composition that includes an acid-labile proton-pump inhibitor other than pantoprazole, an alkaline pellet or tablet core, at least one water-insoluble intermediate layer which controls the release of the active ingredient, and an outer enteric layer which is soluble in the intestine. The subcoating is described as controlling the release of the active ingredient and thereby the active ingredient is released in a modified release manner, i.e., part of the active ingredient is released in immediate manner and part is released in controlled manner.

U.S. Patent No. 5,877,192 discloses the use of the (-)-enantiomer of omeprazole (esomeprazole), or a pharmaceutically acceptable salt thereof, in the treatment of gastric acid related diseases as a means to decrease individual variation in plasma levels when compared to omeprazole. The use of the (-)-enantiomer of omeprazole is used to increase the average plasma levels (AUC) of the substance when compared to those of racemic omeprazole; thereby imparting a higher dose efficiency.

According to the prior art, formulating benzimidazole compounds with the alkaline core being directly coated with an enteric coating without a separating coat was tried with little success with respect to producing stable formulations of benzimidazole compounds. For example, WO 00/78284 discloses a formulation containing a benzimidazole compound without a separating layer. These formulations disclose the use of a neutralized enteric coating applied as a solution with a pH value of at least 6.5 and more preferably in a range of from about 7 to about 10. The enteric coating is applied directly to the benzimidazole derivative substrate. This solution, with the optional addition of a plasticizer, can be directly coated onto the substrate without any need for an intermediate layer.

U.S. Patent No. 6,602,522 discloses a stable pharmaceutical composition for an orally administered acid-labile compound used as an active ingredient. The composition includes a tableted core and a single layer of coating on the tableted core, the coating including an enteric coating agent. The tableted core includes an uncoated granulation of a therapeutically effective amount of the active ingredient, an optional surface active agent, a pharmaceutically acceptable alkaline agent, at least one water-soluble binder, and at least one water-insoluble binder. The patent also discloses a tableted core with an alkaline medium and an enteric coating layered directly on the tableted core.

Later efforts to stabilize benzimidazole compounds were based on the use of an acidic core with a separating layer made up of water-soluble polymers and other excipients.

U.S. Patent No. 5,385,739 discloses a stable formulation of omeprazole microgranules containing a neutral core of sugar and starch and an active layer consisting of a dilution of omeprazole in mannitol, in substantially equal amounts. The active omeprazole layer contains about 10% by weight of carboxymethylstarch and about 5% by weight of a sodium lauryl sulfate surface-active compound. The dilution of omeprazole in mannitol is applied to the neutral core by means of hydroxypropyl methylcellulose as a high viscosity binder.

U.S. Patent No. 5,626,875 discloses the use of an inert sugar/starch spherical core coated with a first layer made up of a mixture of the benzimidazole compound, a water-soluble inert polymer and non-alkaline reacting pharmaceutical acceptable excipients. The first layer is coated with a second isolation layer formed by water-soluble polymers and non-alkaline reacting pharmaceutically accepted excipients. A third layer consisting of an enteric coating is applied over the second layer.

U.S. Patent Application No. 20030118650 discloses a tableted oral pharmaceutical dosage form that is covered by an enteric coating and consists of a plurality of units that contain a benzimidazole compound labile in an acid medium as the active principle. The plurality of units contain: i) an inert core; ii) an active layer deposited on the inert core i) and made up of a benzimidazole compound labile in an acid medium, a non-alkaline water-soluble inert polymer and one or more pharmaceutically acceptable inert excipients; and iii) an intermediate layer consisting of an inert non-alkaline coating formed from a non-alkaline,

water-soluble inert polymer and one or more pharmaceutically acceptable inert excipients. The intermediate layer is disposed over the active layer ii) that covers the inert core i).

U.S. Patent No. 5,626,875 and U.S. Patent Application No. 20030118650 thus use an intermediate layer made of a non-alkaline water-soluble inert polymer along with one or more pharmaceutically acceptable inert excipients.

U.S. Patent No. 6,159,499 discloses a composition that is described as being substantially free of alkaline-reacting compounds. The composition includes (a) a core containing an acid-labile benzimidazole active principle; (b) an intermediate layer surrounding the core; and (c) an enteric layer surrounding the intermediate layer. The core includes a plurality of nuclei and the active principle mixed together and then compressed together. The active principle is described as not being in the form of an alkaline salt. This patent also discloses a process for preparing stable oral dosage form of benzimidazole compounds which are free from alkaline reacting compounds. The process includes the steps of (i) mixing a plurality of nuclei with an active principle; (ii) compressing the product of step (i) to form a core comprising the active principle; (iii) coating the core with an intermediate layer; and (iv) coating the product from step (iii) with an enteric layer.

U.S. Patent No. 6,207,198 discloses a stable drug composition that includes (a) a core containing an acid-labile omeprazole active principle; (b) an intermediate layer that includes at least one polymer; and (c) an enteric layer. The composition is described as being free of alkaline-reacting compounds. The core is made up of pharmaceutically inert nuclei and the active ingredient, both of which are compressed together. The omeprazole active principle is described as not being in the form of an alkaline salt. The polymer of the intermediate layer is described as being selected from sugars, polyethylene glycol, polyvinylpyrrolidone, poly (vinyl alcohol), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, and mixtures thereof.

WO 99/61022 discloses a stable oral pharmaceutical composition in the form of a mixture containing a substituted pyridyl sulfinyl benzimidazole having gastric acid secretion inhibitory activity and a carrier. The carrier includes at least one polymer that is at least partially made up of vinylpyrrolidone monomeric units. Also disclosed is the use of a mixture of benzimidazole compounds with at least one polymer containing vinylpyrrolidone

monomeric units, the mixture being free of any alkaline reacting compounds to stabilize benzimidazole compounds. The formulation is in the form of a premix which is not compressed to facilitate the manufacturing operations.

U.S. Patent Application 2002128293 teaches a stable oral pharmaceutical composition containing omeprazole and a pharmaceutically acceptable carrier that includes at least one water-insoluble polymer that is at least partially made up of vinylpyrrolidone. The application discloses cross-linked polyvinyl pyrrolidone as the water-insoluble polymer that acts as disintegrant. As described below, the inventors have developed a formulation that does not include such a vinylpyrrolidone polymer with disintegrating properties in the separating layer.

There are various drawbacks associated with the prior art formulations with respect to the efficient stabilization of the composition, cost and ease of manufacturing, and environment concerns with the use of organic solvents. The present invention relates to the stable oral benzimidazole compositions which overcome the problems associated with prior art.

Summary of the Invention

In one general aspect there is provided a stable oral benzimidazole pharmaceutical composition. The composition includes a core, a separating layer, and an enteric coating. The core includes a benzimidazole compound, a substantially water-soluble material and, optionally, one or more pharmaceutically acceptable excipients, wherein the core is not alkaline. The separating layer surrounds the core and includes a substantially water-soluble material and, optionally, one or more pharmaceutically acceptable excipients. The enteric coating surrounds the separating layer. At least one of the core and the separating layer includes the substantially water-soluble material without any pharmaceutically acceptable excipients.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the benzimidazole compound may be selected from one or more of omeprazole, lansoprazole, pantoprazole, rabeprazole, and single enantiomers thereof. The one or more pharmaceutically acceptable excipients may be selected from one or more diluents, disintegrants, binders and lubricants.

The diluent may be selected from one or more of sugars, sugar alcohols, cellulose derivatives, and starches. The sugar may be selected from dextrose, glucose and lactose. The sugar alcohol may be selected from sorbitol, xylitol and mannitol. The cellulose derivative may be selected from powdered cellulose and microcrystalline cellulose. The starch may be selected from corn starch, pregelatinized starch, and maize starch. The disintegrant may be selected from one or more of sodium starch glycolate, croscarmellose sodium, and corn starch.

The binder may be selected from one or more of cellulose derivatives, gums, water-soluble vinylpyrrolidone polymers, and sugars. The cellulose derivatives may be one or more of hydroxypropylmethyl cellulose, hydroxypropyl cellulose and methylcellulose. The gums may be one or more of xanthan gum, gum acacia and tragacanth. The water-soluble vinylpyrrolidone polymers may be one or more of polyvinylpyrrolidone and copolymers of vinylpyrrolidone and vinyl acetate. The sugars may be one or more of sorbitol and mannitol.

The lubricant may be one or more of magnesium stearate, talc, sodium stearyl fumarate, and colloidal silicon dioxide. The substantially water-soluble material may be one or more of a substantially water-soluble polymer and a substantially water-soluble excipient. The water-soluble polymer may be selected from one or more of hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, sodium alginate, sodium carboxymethyl cellulose, and copolymer of vinylpyrrolidone and vinyl acetate. The water-soluble excipient may be one or more of lactose, mannitol, sorbitol, sucrose and glucose.

The core may include the substantially water-soluble material without any pharmaceutically acceptable excipients. The separating layer may include the substantially water-soluble material without any pharmaceutically acceptable excipients.

In another general aspect there is provided a stable oral benzimidazole pharmaceutical composition. The pharmaceutical composition includes a core and an enteric coating. The core contains a benzimidazole compound, a substantially water-soluble material, and, optionally, one or more pharmaceutically acceptable excipients, wherein the core is not alkaline. The enteric coating surrounds and is directly in contact with the core. The formulation is devoid of a separating layer between the core and the enteric coating.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the benzimidazole compound may be selected from one or more of omeprazole, lansoprazole, pantoprazole, rabeprazole, and single enantiomer thereof. The one or more pharmaceutically acceptable excipients of the core may be selected from one or more of diluents, disintegrants, binders, and lubricants.

The diluent may be selected from one or more of sugars, sugar alcohols, cellulose derivatives, and starches. The sugar may be selected from dextrose, glucose and lactose. The sugar alcohol may be selected from sorbitol, xylitol, and mannitol. The cellulose derivative may be selected from powdered cellulose and microcrystalline cellulose. The starch may be selected from corn starch, pregelatinized starch, and maize starch. The disintegrant may be selected from one or more of sodium starch glycolate, croscarmellose sodium, and corn starch. The binder may be selected from one or more of cellulose derivatives, gums, water-soluble vinylpyrrolidone polymers, and sugars. The cellulose derivatives may be one or more of hydroxypropylmethyl cellulose, hydroxypropyl cellulose and methylcellulose. The gums may be one or more of xanthan gum, gum acacia and tragacanth. The water-soluble vinylpyrrolidone polymers may be one or more of polyvinylpyrrolidone and copolymers of vinylpyrrolidone and vinyl acetate. The sugars may be one or more of sorbitol and mannitol.

The lubricant may be one or more of magnesium stearate, talc, sodium stearyl fumarate, and colloidal silicon dioxide.

In another general aspect, there is provided a process for the preparation of a stable oral benzimidazole pharmaceutical composition. The process includes preparing a core, coating the core with a separating layer, and coating either the core or the separating layer with an enteric layer. The core is prepared by dispersing a benzimidazole compound, a substantially water-soluble material and, optionally, one or more pharmaceutically acceptable excipients in an aqueous medium to obtain a dispersion, spray drying the dispersion, and mixing with the one or more optional pharmaceutically acceptable excipients and compressing. The core is coated with a separating layer formed by a substantially water soluble material and, optionally, pharmaceutically acceptable excipients. At least one of the core and the separating layer includes the substantially water-soluble material without any pharmaceutically acceptable excipients.

Embodiments of the process may include one or more of the following features. For example, the benzimidazole compound may be selected from one or more of omeprazole, lansoprazole, pantoprazole, rabeprazole, and single enantiomers thereof. The one or more pharmaceutically acceptable excipients of the core may be selected from one or more of diluents, disintegrants, binders, and lubricants.

The diluent may be selected from one or more of sugars, sugar alcohols, cellulose derivatives, and starches. The disintegrant may be selected from one or more of sodium starch glycolate, croscarmellose sodium, and corn starch. The binder may be selected from one or more of cellulose derivatives, gums, water-soluble vinylpyrrolidone polymers, and sugars. The lubricant may be one or more of magnesium stearate, talc, sodium stearyl fumarate, and colloidal silicon dioxide.

In another general aspect there is provided a method inhibiting gastric acid secretion. The method includes administering a pharmaceutical composition that includes (a) a core comprising a benzimidazole compound, a substantially water-soluble material and, optionally, one or more pharmaceutically acceptable excipients, wherein the core is not alkaline; (b) a separating layer surrounding the core and comprising a substantially water-soluble material and, optionally, one or more pharmaceutically acceptable excipients, and (c) an enteric coating surrounding the separating layer. At least one of the core and the separating layer includes the substantially water-soluble material without any pharmaceutically acceptable excipients.

Embodiments of the method may include one or more of the following features or any of the features described herein. For example, the benzimidazole compound may be selected from one or more of omeprazole, lansoprazole, pantoprazole, rabeprazole, and single enantiomers thereof.

In another general aspect there is provided a method inhibiting gastric acid secretion. The method includes administering a pharmaceutical composition that includes (a) a core containing a benzimidazole compound, a substantially water-soluble material, and, optionally, one or more pharmaceutically acceptable excipients, wherein the core is not alkaline, and (b) an enteric coating surrounding and directly in contact with the core, wherein the formulation is devoid of a separating layer between the core and the enteric coating.

Embodiments of the method may include one or more of the following features or any of the features described herein. For example, the benzimidazole compound may be selected from one or more of omeprazole, lansoprazole, pantoprazole, rabeprazole, and single enantiomers thereof.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

In seeking to develop stable benzimidazole dosage forms, the inventors have developed a number of stable dosage forms and processes for their preparation. For example, the inventors have developed a stable benzimidazole dosage form that includes a core, a separating layer, and an enteric coating. The core includes a benzimidazole compound, a water-soluble material, and optional pharmaceutically accepted excipients. The core is characterized as not being alkaline. The separating layer is deposited or otherwise coated on the core and includes a water-soluble material and, optionally, one or more pharmaceutically accepted excipient. The enteric coating surrounds the separating layer. At least one of the core or the separating layer has a water-soluble material without additional pharmaceutically acceptable excipients.

The inventors also have developed a stable benzimidazole dosage form that includes a core and an enteric coating that is deposited or otherwise coated directly on the core. The core contains a benzimidazole compound, a water-soluble material and, optionally, one or more pharmaceutically acceptable excipients. Moreover, the core is characterized as being not alkaline.

One process to formulate the stable benzimidazole formulation includes preparing a core and coating the core. To prepare the core, a benzimidazole compound, a water-soluble material and, optionally, one or more pharmaceutically acceptable excipients are dispersed in purified water to obtain a dispersion. The dispersion is spray dried, mixed with optional pharmaceutically acceptable excipients, and compressed to form cores. The core then is coated with a separating layer that is formed from substantially water-soluble material and optional pharmaceutically acceptable excipients. The coated core then is coated with an

enteric coating. Alternatively, the cores may be enteric coated without including the separating layer.

Suitable benzimidazole compounds include any substituted benzimidazole compound that is capable of inhibiting gastric acid secretion by any mechanism and thus having utility in treating various gastrointestinal disorders. The benzimidazole compounds may include, for example, one or more of omeprazole, lansoprazole, rabeprazole, pantoprazole, leminoprazole, pariprazole, single enantiomers thereof, pharmaceutically acceptable salts, solvates, hydrates, or mixtures thereof. The benzimidazole compounds may be in the crystalline or amorphous salt form. The amount of benzimidazole compound may vary from about 1% to about 80%, and preferably from about 5% to about 35% based on the weight of the formulation.

The core as used herein refers to any structure that is enclosed or surrounded by a separating coating or equivalent, or where the separating coating is absent, enclosed or surrounded by an enteric coating. The core may be in the form of a tablet, pellet, capsule, powder or mixture thereof. The term 'tablet' as used herein may include one or more of minitablets, microtablets, or tablets. The term 'pellets' as used herein may include one or more of granules, beads, pellets, slugs or mixtures thereof. The core is preferably non-alkaline. The core may contain one or more pharmaceutically acceptable excipients, including one or more of binders, diluents, disintegrants, lubricants/glidants and solubilizers/wetting agents.

The benzimidazole compound in the core may be amorphous or crystalline. The benzimidazole compound may also be spray dried with water soluble polymers and incorporated in the core. The core may contain one or more pre-layers of water soluble polymers between the inert nucleus and drug containing layer. These one or more pre-layers are different from the separating layer (or subcoat).

Suitable diluents include one or more of sugars, such as dextrose, glucose, and lactose; sugar alcohols such as sorbitol, xylitol, and mannitol; cellulose derivatives such as powdered cellulose and microcrystalline cellulose; starches such as corn starch, pregelatinized starch, and maize starch. The preferred range of diluents in the formulation depends on the type of formulations to be prepared as disclosed in the various examples contained herein.

Suitable binders include one or more of cellulose derivatives such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, and methylcellulose; gums such as xanthan gum, gum acacia, and tragacanth; water-soluble vinylpyrrolidone polymers such as polyvinylpyrrolidone and copolymers of vinylpyrrolidone and vinyl acetate; and sugars such as sorbitol, mannitol or such like. The preferred range of binders in the formulation depends on the type of formulations to be prepared as disclosed in various examples contained herein.

Suitable disintegrants may include one or more of sodium starch glycolate, croscarmellose sodium, corn starch, and other suitable disintegrants. Suitable wetting agents include one or more of sodium lauryl sulphate, polysorbate 80, and equivalents. Suitable lubricants/glidants include one or more of magnesium stearate, talc, sodium stearyl fumarate, colloidal silicon dioxide and equivalents. The preferred ranges of disintegrants, wetting agents, and lubricants/glidants in the formulation depends on the type of formulations to be prepared as disclosed in various examples contained herein.

The separating layer as used herein refers to the layer that separates the core from the enteric coating. The separating layer is made up of substantially water soluble materials which is capable of dissolving or forming a gel upon or after contact with water. Such materials may include substantially water-soluble polymers and/or substantially water-soluble excipients. In the case in which the capsule shell acts as a separating layer, an additional application of one or more separating layers is optional. The enteric coating can directly be layered on the capsule shell in such a formulation. The substantially water-soluble excipients may be selected from glucose, lactose, mannitol, sorbitol, sucrose, dextrose or equivalents. The substantially water-soluble polymers may be selected from hydroxypropylmethylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, sodium alginate, sodium carboxymethyl cellulose, copolymer of vinylpyrrolidone and vinyl acetate. Preferably, such polymers are hydroxypropylmethylcellulose, hydroxypropyl cellulose or polyvinylpyrrolidone. The range of the substantially water-soluble polymers in the formulation depends on the type of formulations prepared and will be apparent to one skilled in the art based on the various examples disclosed in the specification.

The enteric coating may include one or more of cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate,

carboxymethylethylcellulose, methacrylic acid methyl esters/methacrylic acid copolymers, such as compounds known under the trademarks of Eudragit NE30D, Eudragit L, Eudragit S, Eudragit L 100 55 and marketed by Rohm Pharma, and mixtures thereof. The enteric coating may also contain plasticizers such as triacetin, triethyl citrate, tributyl sebecate, diethyl phthalate, polyethylene glycol and inert excipients such as talc, titanium dioxide, colloidal silicon dioxide, hydroxypropyl methylcellulose, crospovidone and the like.

The following examples illustrate stable oral benzimidazole compositions and processes of making the compositions as disclosed in the various embodiments discussed throughout the specification. The example are merely provided to illustrate the composition and processes for their preparation and are not intended to be limiting. The obvious variations of these compositions are contemplated to be within the scope of the present invention and the appended claims.

Example 1:

S. No	Ingredients	Quantity (mg/unit)
A)	**Drug layering on inert tablet core**	
1	Inert tablet core of Mannitol/Lactose/Microcrystalline cellulose (Diameter of about 7.0-9.0 mm)	145.0
2	Omeprazole	20.0
3	Polyvinyl pyrrolidone (PVP-K30)/Hydroxypropyl cellulose (HPC-L)/Hydroxypropyl methylcellulose (HPMC)/Mannitol	7.0
4	#Ammonium hydroxide	qs
5	Purified water	qs
B)	**Separating layer (optional)**	
1	Hydroxypropyl cellulose (HPC-L)/ Hydroxypropyl methylcellulose (HPMC)/Mannitol	8.6
2	Purified water	qs
C)	**Enteric layer**	
1	Acryl EZE ™*	18.0
2	Purified water	qs
	OR	
1	Eudragit L30D-55	38.15
2	Polyethylene glycol 300	1.15
3	Talc	4.06
4	Titanium dioxide	1.35
5	Purified water	qs

evaporates during processing

*Acryl EZE ™ is a registered trademark of Colorcon and is a type of ready to disperse enteric coating formulation.

Procedure:

PVP-K30/HPC-L/HPMC/Mannitol (one or mixtures there of) was dissolved in water, and to this ammonium hydroxide was added. To the above mixture omeprazole was added and dispersed. The dispersion was applied to the inert tablet using a conventional coating machine. The benzimidazole tablets thus prepared were coated with suitable polymer/excipient using a conventional coating machine. Finally, the tablets were enteric coated with the enteric layer formulation.

Example 2:

S. No	Ingredients	Quantity (mg/unit)
A)	**Core pellet**	
1	Non-pariel seeds (Microcrystalline cellulose / Sugar)	190.68
B)	**Prelayering (optional)**	
1	Hydroxypropyl cellulose (HPC-L) / Hydroxypropyl methylcellulose (HPMC)	9.52
2	Purified water	qs
C)	**Drug layer**	
1	Esomeprazole	40.0
2	Hydroxypropyl cellulose (HPC-L) / Mannitol	20.0
3	#Ammonium hydroxide	qs
4	Purified water	qs
D)	**Separating layer**	
1	Hydroxypropyl cellulose (HPC-L) / Hydroxypropyl methylcellulose (HPMC)	26.0
2	Purified water	qs
E)	**Enteric layer**	
1	*Acryl EZE ™	85.80
2	Purified water	qs
	or	
1	Eudragit L30D-55	114.39
2	Polyethylene glycol 300	3.43
3	Talc	12.12
4	Titanium dioxide	4.04
5	Purified water	qs

evaporates during processing

*Acryl EZE ™ is a registered trademark of Colorcon and is a type of ready-to-disperse enteric coating formulation.

Procedure:

HPMC/HPC-L was dissolved in water and applied on Non Pariel seeds. HPC-L/Mannitol was dissolved under stirring in purified water. To the above mixture ammonium hydroxide was added, with continuous stirring. Esomeprazole was dispersed in the mixture thus prepared under constant stirring. The non-pariel seeds were coated with the esomeprazole dispersion in a Fluid Bed Processor to form pellets. The pellets then were coated with suitable polymer/excipient and then enteric material using a Fluid Bed Processor.

Example 3:

S. No	Ingredients	Quantity (mg/unit)
A)	**Drug layering on inert tablet core**	
1	Inert tablet core of mannitol (Diameter of about 2.0-5.0mm)	57.5
2	Rabeprazole	10.0
3	Polyvinyl pyrrolidone (PVP-K30) / Hydroxypropyl cellulose (HPC-L) / Hydroxypropyl methylcellulose (HPMC)	2.25
4	#Ammonium hydroxide	qs
5	Purified water	qs
B)	**Separating layer**	
1	Hydroxypropyl cellulose (HPC-L) / Hydroxypropyl methylcellulose (HPMC)	2.25
2	Purified water	qs
C)	**Enteric layer**	
1	*Acryl EZE ™	5.0
2	Purified water	qs

evaporates during processing

*Acryl EZE ™ is a registered trademark of Colorcon, is a type of ready to disperse enteric coating formulation.

Procedure:

PVP-K30/HPC-L/HPMC was dissolved in water and to this ammonium hydroxide was added. To the above mixture rabeprazole was added and dispersed. The dispersion was applied on inert tablet using conventional coating machine. Prepared benzimidazole tablets were coated with suitable polymer using conventional coating machine. The tablets then were enteric coated with Acryl EZE. Multiple tablets were filled in hard gelatin capsules.

Example 4:

S.No	Ingredients	Quantity (mg/unit)
A)	**Drug Layering**	
1	Non-pariel seeds	160
2	Lansoprazole	30
3	Hydroxypropyl methylcellulose	17
4	Purified water	q.s.
B)	**Separating layer**	
1	Hydroxypropyl methylcellulose	38
2	Talc	8
3	Titanium dioxide	11
4	Purified water	q. s.
C)	**Enteric coating**	
1	Hydroxypropyl methylcellulose phthalate / Eudragit L100-55 / Eudragit L30D-55	48
2	Polyethylene glycol 300	9.2
3	Talc	20.5
4	Titanium dioxide	0.75
5	Purified water	q. s.
6	Acetone	q. s.

Procedure:

Drug layering

1. Hydroxypropyl methylcellulose was dissolved in water followed by dispersion of lansoprazole.
2. Non-pariel seeds were loaded in fluid bed processor followed by spraying the dispersion of step 1 to obtain drug-layered pellets.

Separating layer

1. Hydroxypropyl methylcellulose was dissolved in water followed by dispersion of talc and titanium dioxide.
2. The drug-layered pellets were loaded in fluid bed processor followed by coating with the solution of step 1 above.

Enteric coating

Preparation of Hydroxypropyl methylcellulose phthalate coating dispersion:

1. Talc, Titanium dioxide and Polyethylene glycol 300 were dispersed in acetone.
2. Hydroxypropyl methylcellulose phthalate was dissolved in acetone
3. The dispersion of step 1 was added to the dispersion of step 2 followed by water addition and mixing.

The barrier-coated pellets were coated with the above enteric coating dispersion and the enteric-coated pellets were filled in hard gelatin capsules.

Example 5:

S.No	Ingredients	Quantity (mg/unit)
A)	**Drug Layering**	
1	Non-pariel seeds	160
2	Lansoprazole	30
3	Hydroxypropyl methylcellulose	17
4	Purified water	q.s.
B)	**Separating layer**	
1	Hydroxypropyl methylcellulose	57
2	Purified water	q. s.
C)	**Enteric coating**	
1	Hydroxypropyl methylcellulose phthalate / Eudragit L100-55 / Eudragit L30D-55	48
2	Polyethylene glycol 300	9.2
3	Talc	20.5
4	Titanium dioxide	0.75
5	Purified water	q. s.
6	Acetone	q. s.

The procedure described above for Example 4 was followed for Example 5..

Example 6:

S.No	Ingredients	Quantity (mg / unit)
A)	**Drug Layering**	
1	Sugar spheres	160
2	Lansoprazole (micronized)	30
3	Hydroxypropyl methylcellulose	17
4	Purified water	q.s.
B)	**Separating layer**	
1	Hydroxypropyl methylcellulose	32.2
2	Talc	13.8
3	Titanium dioxide	11.0
4	Purified water	q. s.
C)	**Enteric coating**	
1	Methacrylic acid-Ethylacrylate copolymer (1:1) 30% Dispersion	170
2	Polyethylene glycol 300	5.1
3	Talc	18
4	Titanium dioxide	5.9
5	Purified water	q. s.
D)	**Blending**	
1	Talc	0.3
2	Colloidal silicon dioxide	0.3

Procedure:

Drug layering

1. Hydroxypropyl methylcellulose was dissolved in water followed by dispersion of lansoprazole.
2. Sugar spheres were loaded in fluid bed processor followed by spraying dispersion of step 1 to obtain drug-layered pellets.

Separating layer

1. Hydroxypropyl methylcellulose was dissolved in water followed by dispersion of talc and titanium dioxide.
2. The drug-layered pellets were loaded in fluid bed processor followed by coating with solution of step 1 above.

Enteric coating

Preparation of Hydroxypropyl methylcellulose phthalate coating dispersion:

1. Talc, Titanium dioxide and Polyethylene glycol 300 were dispersed in water.
2. The dispersion of step 1 above was added to the Methacrylic acid:Ethylacrylate copolymer dispersion and stirred for 30 min.

The barrier-coated pellets were coated with the above enteric coating dispersion and the enteric-coated pellets were filled into hard gelatin capsules.

Example 7:

S.No	Ingredients	Quantity (mg/unit)
A)	**Core pellet**	
1	Non-pariel seeds	130
2	Hydroxypropyl cellulose (HPC-L)	6.5
3	Purified water	qs
B)	**Drug layering**	
1	Omeprazole	40
2	Hydroxypropyl cellulose (HPC-L)	5
3	#Ammonium hydroxide	qs
4	Purified water	q.s.
C)	**Separating layer**	
1	Mannitol	18.15
2	Purified water	q. s.
D)	**Enteric coating**	
1	Eudragit L30D-55	114.39
2	Polyethylene glycol 300	3.43
3	Talc	12.12
4	Titanium dioxide	4.04
5	Purified water	q. s.
6	Colloidal silicon dioxide	0.44

Evaporates during processing

Procedure:

Hydroxypropyl cellulose was dissolved in water and sprayed on non-pariel seeds. Hydroxypropyl cellulose was dissolved under stirring in purified water and then ammonium hydroxide was added under continued stirring. Then omeprazole was dispersed in a prepared mixture under constant stirring. Non-pariel seeds were coated with omeprazole dispersion in a Fluid Bed Processor to obtain pellets. The pellets thus prepared were coated with mannitol

followed by the enteric coating formulation using a Fluid Bed Processor. Finally, the pellets were blended with colloidal silicon dioxide and filled into hard gelatin capsules.

Example 8:

S.No	Ingredients	Quantity (mg/unit)
A)	**Core pellet**	
1	Non-pariel seeds	130
2	Hydroxypropyl cellulose (HPC-L)	4.75
3	Polyethylene glycol 6000	0.47
4	Talc	1.28
5	Purified water	qs
B)	**Drug layering**	
1	Omeprazole	40
2	Hydroxypropyl cellulose (HPC-L)	5
3	#Ammonium hydroxide	qs
4	Purified water	q.s.
C)	**Separating layer**	
1	Mannitol / Hydroxypropyl cellulose (HPC-L)/ Hydroxypropyl methylcellulose (HPMC)	18.15
2	Purified water	q. s.
D)	**Enteric coating**	
1	Eudragit L30D-55	114.39
2	Polyethylene glycol 300	3.43
3	Talc	12.12
4	Titanium dioxide	4.04
5	Purified water	q. s.
6	Colloidal silicon dioxide	0.44

Procedure:

Hydroxypropyl cellulose and polyethylene glycol 6000 were dissolved in water. Talc was dispersed in the above solution and the resulting dispersion was sprayed on to non-pariel seeds. Hydroxypropyl cellulose was dissolved under stirring in purified water followed by the addition of ammonium hydroxide under continued stirring. Omeprazole was dispersed onto the above prepared mixture under constant stirring. The above dispersion then was sprayed onto non-pariel seeds in a fluid bed processor to obtain pellets. The pellets were coated with mannitol/HPC/HPMC followed by the enteric coating formulation using a fluid bed processor. Finally, the pellets were blended with colloidal silicon dioxide and filled into hard gelatin capsules.

Example 9:

S. No	Ingredients	Quantity (mg/unit)
A)	**Spray drying**	
1	Omeprazole	20.0
2	Mannitol	80.0
3	Polyvinyl pyrrolidone (PVP-K30) / Hydroxypropyl cellulose (HPC-L) / Hydroxypropyl methylcellulose (HPMC)	3.0
4	#Ammonium hydroxide	qs
5	Purified water	qs
B)	**Tablet**	
1	Mannitol (Pearlitol SD 200™)	63.5
2	Sodium stearyl fumarate	3.50
C)	**Separating layer (optional)**	
1	Hydroxypropyl cellulose (HPC-L) / Hydroxypropyl methylcellulose (HPMC) / Mannitol	8.5
2	Purified water	qs
D)	**Enteric layer**	
1	Acryl EZE™*	18.0
2	Purified water	qs
	OR	
1	Eudragit L30D-55	38.15
2	Polyethylene glycol 300	1.15
3	Talc	4.06
4	Titanium dioxide	1.35
5	Purified water	qs

Evaporates during processing

*Acryl EZE™ is a registered trademark of Colorcon and is a type of ready-to-disperse enteric coating formulation.

Procedure:

Mannitol and PVP-K30/HPC-L/HPMC were dissolved in water, and to this ammonium hydroxide was added. To the above mixture omeprazole was added and dispersed. The

dispersion then was spray dried and the spray dried granules were mixed with Pearlitol, lubricated with sodium stearyl fumarate to form a blend, and the blend was compressed into tablets. The benzimidazole tablets thus prepared were coated with suitable polymer/excipient using a conventional coating machine. The tablets then were enteric coated with the enteric coating formulation.

Example 10: Enteric-coated minitablets containing pantoprazole.

S.No	Ingredients	Quantity (mg/unit)
A)	**Coating of drug**	
1	Pantoprazole	30
2	Hydroxypropyl methylcellulose (for mixing)	15
3	Hydroxypropyl methylcellulose (for coating)	15
4	Purified water	
B)	**Compression (conversion into mini tablets)**	
1	Coated pantoprazole	60
2	Mannitol	20
3	Crospovidone	157
4	Microcrystalline cellulose	157
5	Talc	2
6	Sodium stearyl fumarate	2
7	Colloidal silicon dioxide	2
C)	**Enteric coating**	
1	Hydroxypropyl methylcellulose phthalate / Eudragit L100-55	21.04
2	Polyethylene glycol 300	4.11
3	Talc	9.19
4	Titanium dioxide	0.35
5	Purified water	q.s.
6	Acetone	q.s.

Procedure:

Coating of Drug

1. Pantoprazole and Hydroxypropyl methylcellulose (for mixing) were mixed and granulated with purified water to obtain a wet mass.
2. The wet mass was passed through 30-mesh screen.
3. Hydroxypropyl methylcellulose (for coating) was dissolved in purified water.
4. The screened mass of step 2 was loaded in a Fluid bed processor and the solution of step 3 was sprayed onto it to obtain coated pantoprazole.

Compression

1. The coated Pantoprazole, Mannitol, Microcrystalline cellulose and Crospovidone were mixed in suitable blender.
2. Magnesium stearate and Colloidal silicon dioxide were added to the blend of step 5.
3. The blend of step 6 was compressed into tablets.

Enteric coating

Preparation of Hydroxypropyl methylcellulose phthalate coating dispersion:

1. Talc, Titanium dioxide and Polyethylene glycol 300 were dispersed in acetone.
2. Hydroxypropyl methylcellulose phthalate was dissolved in acetone
3. The dispersion of step (1) was added to dispersion of step (2) followed by water addition and mixing.

The tablets thus produced were enteric coated with enteric coating dispersion and suitable numbers of tablets as per desired dosage were optionally filled into hard gelatin capsule. While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the invention. Other nonessential ingredients optionally can be added to the blend or mixture for cosmetic, aesthetic and/or manufacturing purposes. These include colorants, diluents, lubricants, and glidants. Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed invention and be so described as a negative limitation. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

We Claim:

1. A stable oral benzimidazole pharmaceutical composition, the composition comprising;

a) a core comprising a benzimidazole compound, a substantially water-soluble material and, optionally, one or more pharmaceutically acceptable excipients, wherein the core is not alkaline;

b) a separating layer surrounding the core and comprising a substantially water-soluble material and, optionally, one or more pharmaceutically acceptable excipients, and

c) an enteric coating surrounding the separating layer,

wherein at least one of the core and the separating layer includes the substantially water-soluble material without any pharmaceutically acceptable excipients.

2. The composition of claim 1, wherein the benzimidazole compound is selected from one or more of omeprazole, lansoprazole, pantoprazole, rabeprazole, and single enantiomer thereof.

3. The composition of claim 1, wherein the one or more pharmaceutically acceptable excipients are selected from one or more diluents, disintegrants, binders and lubricants.

4. The composition of claim 3, wherein the diluent is selected from one or more of sugars, sugar alcohols, cellulose derivatives, and starches.

5. The composition of claim 4, wherein the sugar is selected from one or more of dextrose, glucose and lactose.

6. The composition of claim 4, wherein the sugar alcohol is selected from one or more of sorbitol, xylitol and mannitol.

7. The composition of claim 4, wherein the cellulose derivative is selected from one or more of powdered cellulose and microcrystalline cellulose.

8. The composition of claim 4, wherein the starch is selected from one or more of corn starch, pregelatinized starch, and maize starch.

9. The composition of claim 3, wherein the disintegrant is selected from one or more of sodium starch glycolate, croscarmellose sodium, and corn starch.

10. The composition of claim 3, wherein the binder is selected from one or more of cellulose derivatives, gums, water-soluble vinylpyrrolidone polymers, and sugars.

11. The composition of claim 10, wherein the cellulose derivatives comprise one or more of hydroxypropylmethyl cellulose, hydroxypropyl cellulose and methylcellulose.

12. The composition of claim 10, wherein the gums comprise one or more of xanthan gum, gum acacia and tragacanth.

13. The composition of claim 10, wherein the water-soluble vinylpyrrolidone polymers comprise one or more of polyvinylpyrrolidone and copolymers of vinylpyrrolidone and vinyl acetate.

14. The composition of claim 10, wherein the sugars comprise one or more of sorbitol and mannitol.

15. The composition of claim 3, wherein the lubricant comprises one or more of magnesium stearate, talc, sodium stearyl fumarate, and colloidal silicon dioxide.

16. The composition of claim 1, wherein the substantially water-soluble material comprises one or more of a substantially water-soluble polymer and a substantially water-soluble excipient.

17. The composition of claim 16, wherein the water-soluble polymer is selected from one or more of hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, sodium alginate, sodium carboxymethyl cellulose, and copolymer of vinylpyrrolidone and vinyl acetate.

18. The composition of claim 17, wherein the water-soluble excipient comprises one or more of lactose, mannitol, sorbitol, sucrose and glucose.

19. The composition of claim 1, wherein the core includes the substantially water-soluble material without any pharmaceutically acceptable excipients.

20. The composition of claim 1, wherein the separating layer includes the substantially water-soluble material without any pharmaceutically acceptable excipients.

21. A stable oral benzimidazole pharmaceutical composition, the composition comprising:

a) a core containing a benzimidazole compound, a substantially water-soluble material, and, optionally, one or more pharmaceutically acceptable excipients, wherein the core is not alkaline, and

b) an enteric coating surrounding and directly in contact with the core, wherein the formulation is devoid of a separating layer between the core and the enteric coating.

22. The composition of claim 21, wherein the benzimidazole compound is selected from one or more of omeprazole, lansoprazole, pantoprazole, rabeprazole, and single enantiomer thereof.

23. The composition of claim 21, wherein the one or more pharmaceutically acceptable excipient of the core are selected from one or more of diluents, disintegrants, binders, and lubricants.

24. The composition of claim 23, wherein the diluent is selected from one or more of sugars, sugar alcohols, cellulose derivatives, and starches.

25. The composition of claim 24, wherein the sugar is selected from one or more of dextrose, glucose and lactose.

26. The composition of claim 24, wherein the sugar alcohol is selected from one or more of sorbitol, xylitol, and mannitol.

27. The composition of claim 24, wherein the cellulose derivative is selected from one or more of powdered cellulose and microcrystalline cellulose.

28. The composition of claim 24, wherein the starch is selected from one or more of corn starch, pregelatinized starch, and maize starch.

29. The composition of claim 23, wherein the disintegrant is selected from one or more of sodium starch glycolate, croscarmellose sodium, and corn starch.

30. The composition of claim 32, wherein the binder is selected from one or more of cellulose derivatives, gums, water-soluble vinylpyrrolidone polymers, and sugars.

31. The composition of claim 30, wherein the cellulose derivatives comprise one or more of hydroxypropylmethyl cellulose, hydroxypropyl cellulose and methylcellulose.

32. The composition of claim 30, wherein the gums comprise one or more of xanthan gum, gum acacia and tragacanth.

33. The composition of claim 30, wherein the water-soluble vinylpyrrolidone polymers comprise one or more of polyvinylpyrrolidone and copolymers of vinylpyrrolidone and vinyl acetate.

34. The composition of claim 30, wherein the sugars comprise one or more of sorbitol and mannitol.

35. The composition of claim 23, wherein the lubricant comprises one or more of magnesium stearate, talc, sodium stearyl fumarate, and colloidal silicon dioxide.

36. A process for the preparation of a stable oral benzimidazole pharmaceutical composition, the process comprising:

a) preparing a core formed by dispersing a benzimidazole compound, a substantially water-soluble material and, optionally, one or more pharmaceutically acceptable excipients in an aqueous medium to obtain a dispersion, spray drying the dispersion, and mixing with the one or more optional pharmaceutically acceptable excipients and compressing;

b) coating the core with a separating layer formed by a substantially water soluble material and optional pharmaceutically acceptable excipients; and

c) coating the product of step a) or b) with an enteric coating,

wherein at least one of the core and the separating layer includes the substantially water-soluble material without any pharmaceutically acceptable excipients.

37. The process of claim 36, wherein the benzimidazole compound is selected from one or more of omeprazole, lansoprazole, pantoprazole, rabeprazole, and single enantiomers thereof.

38. The process of claim 36, wherein the one or more pharmaceutically acceptable excipients of the core are selected from one or more of diluents, disintegrants, binders, and lubricants.

39. The process of claim 38, wherein the diluent is selected from one or more of sugars, sugar alcohols, cellulose derivatives, and starches.

40. The process of claim 38, wherein the disintegrant is selected from one or more of sodium starch glycolate, croscarmellose sodium, and corn starch.

41. The process of claim 38, wherein the binder is selected from one or more of cellulose derivatives, gums, water-soluble vinylpyrrolidone polymers, and sugars.

42. The process of claim 38, wherein the lubricant comprises one or more of magnesium stearate, talc, sodium stearyl fumarate, and colloidal silicon dioxide.

43. A method inhibiting gastric acid secretion, the method comprising administering a pharmaceutical composition that includes:

a) a core comprising a benzimidazole compound, a substantially water-soluble material and, optionally, one or more pharmaceutically acceptable excipients, wherein the core is not alkaline;

b) a separating layer surrounding the core and comprising a substantially water-soluble material and, optionally, one or more pharmaceutically acceptable excipients, and

c) an enteric coating surrounding the separating layer,

wherein at least one of the core and the separating layer includes the substantially water-soluble material without any pharmaceutically acceptable excipients.

44. The method of claim 43, wherein the benzimidazole compound is selected from one or more of omeprazole, lansoprazole, pantoprazole, rabeprazole, and single enantiomers thereof.

45. A method inhibiting gastric acid secretion, the method comprising administering a pharmaceutical composition that includes:

a) a core containing a benzimidazole compound, a substantially water-soluble material, and, optionally, one or more pharmaceutically acceptable excipients, wherein the core is not alkaline, and

b) an enteric coating surrounding and directly in contact with the core, wherein the formulation is devoid of a separating layer between the core and the enteric coating.

46. The method of claim 45, wherein the benzimidazole compound is selected from one or more of omeprazole, lansoprazole, pantoprazole, rabeprazole, and single enantiomers thereof.

INTERNATIONAL SEARCH REPORT

Ir onal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/30 A61K9/50 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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